UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/532,975	04/28/2005	Yasumasa Mitani	20078.0005USWO	4649

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BERTAGNA, ANGELA MARIE

ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

<table>
<tr><td rowspan="3">Office Action Summary</td><td>Application No.
10/532,975</td><td>Applicant(s)
MITANI ET AL.</td></tr>
<tr><td>Examiner
ANGELA BERTAGNA</td><td>Art Unit
1637</td></tr>
</table>

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE <u>3</u> MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.
- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on <u>15 January 2009</u>.

2a)☒ This action is **FINAL**.   2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) <u>1-17</u> is/are pending in the application.

    4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) <u>1-17</u> is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

    Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

    Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

    a)☐ All   b)☐ Some * c)☐ None of:

      1.☐ Certified copies of the priority documents have been received.

      2.☐ Certified copies of the priority documents have been received in Application No. _____.

      3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

    * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
    Paper No(s)/Mail Date <u>4/7/09; 1/15/09; 11/12/08; 10/24/08</u>.

4) ☐ Interview Summary (PTO-413)
    Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

U.S. Patent and Trademark Office

PTOL-326 (Rev. 08-06)   **Office Action Summary**   Part of Paper No./Mail Date 20090331

DETAILED ACTION

Status of the Application

1.   Applicant's response filed on January 15, 2009 is acknowledged. Claims 1-17 are

currently pending. In the response, Applicant amended claims 1-3, 6, 9-12, 15, and 17 and

canceled claims 22-23.

The following include new grounds of rejection necessitated by Applicant's amendments

to the claims. Any previously made objections or rejections not reiterated below have been

withdrawn as being obviated by the amendment. Applicant's arguments filed on January 15,

2009 that remain pertinent to the new grounds of rejection have been fully considered, but they

were not persuasive for the reasons set forth in the "Response to Arguments" section. Since the

grounds of rejection presented below were necessitated by Applicant's amendment, this Office

Action is made **FINAL**.

Information Disclosure Statement

2.   Applicant's submission of Information Disclosure Statements on October 24, 2008,

November 12, 2008, January 15, 2009, and April 7, 2009 is acknowledged. The Information

Disclosure Statement filed on November 12, 2008 appears to be a duplicate of the Information

Disclosure Statement filed on September 11, 2008. The references cited on the IDS filed on

September 11, 2008 were considered on October 6, 2008 (see non-final Office Action mailed on

10/24/08). Accordingly, the IDS filed on November 12, 2008 has not been considered.

Claim Rejections - 35 USC § 103

3.　　The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all

obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the

claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c)

and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4.　　Claims 1-7 and 9-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over

Rabbani et al. (EP 0 971 039 A2; cited previously) in view of Notomi et al. (Nucleic Acids

Research 2000; 28(12): e63; cited previously) and further in view of Nagamine (Molecular and

Cellular Probes (June 2002) 16(3):223-229; cited on an IDS).

These claims are drawn to an isothermal nucleic acid amplification method.

Regarding claim 1, Rabbani teaches a method for amplifying a nucleic acid comprising:

(a) annealing a primer to a template nucleic acid and synthesizing a complementary

nucleic acid via primer extension,

wherein the primer comprises in its 3' end portion a sequence (Ac') that hybridizes to a sequence (A) in the 3'end portion of the target nucleic acid, and a sequence (B') located 5' of (Ac') that hybridizes to the complementary sequence (Bc) of a sequence (B) positioned 5' of sequence (A) in the target nucleic acid (see Example 1 on page 21, especially paragraphs 120-121, where the FC and RC primers of Rabbani are taught; see also Figure 1, steps 1-2)

wherein in the absence of an intervening sequence between (Ac') and (B'), (X-Y)/X is between –1.00 and 1.00, where X is the number of bases in sequence (Ac') and Y is the number of bases in the region flanked by sequences (A) and (B) on the target nucleic acid sequence (see Example 1 on page 21, paragraphs 117-118, where the FC and RC primers have an (Ac') region of 19 or 20 nucleotides and the region flanked by sequences A and B is 0 nucleotides, since there is no intervening sequence between them. Therefore, (X-Y)/X = 1 and X+Y = 19 or 20)

(b) hybridizing sequence (B') with sequence (Bc) on the newly synthesized strand, thereby allowing sequence (A) on the target strand to be single-stranded (see Figure 1, step 3)

(c) annealing another primer of step (a) to the single-stranded sequence (A) on the target generated in step (d) and conducting a strand displacement reaction, thereby displacing the complementary nucleic acid synthesized in step (c) (see Figure 1, steps 4-5).

Regarding claim 2, Rabbani teaches that the double-stranded nucleic acid obtained in step (e) is used repeatedly in step (d) (see Figure 1 and paragraph 47).

Regarding claims 3 and 12, Rabbani teaches that the method is conducted isothermally (see paragraphs 46, 51, and 121).

Regarding claims 4 and 13, Rabbani teaches use of the Bst DNA polymerase, which has strand-displacing ability (paragraph 120).

Regarding claims 5 and 14, Rabbani teaches that the method further comprises a step of

synthesizing cDNA with a reverse transcriptase from an RNA template (paragraph 111).

Regarding claims 6, 7, 15, and 16, Rabbani teaches conducting the method in the

presence of a melting temperature adjusting agent, specifically formamide or DMSO (paragraph

39).

Regarding claim 9, Rabbani teaches a method for amplifying a target nucleic acid in a

double-stranded template nucleic acid comprising:

(a) annealing first and second primers to first and second template nucleic acids of a

double-stranded template nucleic acid and synthesizing first and second complementary strands

via primer extension (see paragraphs 117-118; see also Figure 1, steps 1-2 for a schematic of

how the primers anneal to the target. Although Figure 1 shows the reactions occurring on only

one strand, when both the FC and RC primer are used with a double-stranded template as taught

by Rabbani in Example 1, each of the primers inherently undergoes the reactions outlined in

Figure 1 on a different strand of the template; see also paragraph 77, where Rabbani expressly

teaches conducting the amplification method using two stem-loop primers each of which is

complementary to a different strand of a double-stranded DNA template),

wherein the first primer comprises in its 3' end portion a sequence (Ac') that hybridizes

to a sequence (A) in the 3'end portion of the target nucleic acid, and a sequence (B') located 5'

of (Ac') that hybridizes to the complementary sequence (Bc) of a sequence (B) positioned 5' of

sequence (A) in the target nucleic acid (see Example 1 on page 21, where the FC and RC primers

of Rabbani are taught; see also Figure 1 for a schematic of the primers binding to a target;

paragraphs 77 & 177 teach the use of double-stranded nucleic acid targets), and

wherein in the absence of an intervening sequence between (Ac') and (B'), (X-Y)/X is between −1.00 and 1.00, where X is the number of bases in sequence (Ac') and Y is the number of bases in the region flanked by sequences (A) and (B) on the target nucleic acid sequence (see Example 1 on page 21, paragraphs 117-118, where the FC and RC primers have an (Ac') region of 19 or 20 nucleotides and the region flanked by sequences A and B is 0 nucleotides, since there is no intervening sequence between them. Therefore, (X-Y)/X = 1 and X+Y = 19 or 20), and

wherein the second primer comprises in its 3' end portion a sequence (Cc') that hybridizes to a sequence (C) in the 3'end portion of the target nucleic acid, and a sequence (D') located 5' of (Cc') that hybridizes to the complementary sequence (Dc) of a sequence (D) positioned 5' of sequence (C) in the target nucleic acid (see Example 1 on page 21, where the FC and RC primers of Rabbani are taught; see also Figure 1 for a schematic of the primers binding to a target)

wherein in the absence of an intervening sequence between (Cc') and (D'), (X-Y)/X is between −1.00 and 1.00, where X is the number of bases in sequence (Cc') and Y is the number of bases in the region flanked by sequences (C) and (D) on the target nucleic acid sequence (see Example 1 on page 21, paragraphs 117-118, where the FC and RC primers have an (Cc') region of 19 or 20 nucleotides and the region flanked by sequences C and D is 0 nucleotides, since there is no intervening sequence between them. Therefore, (X-Y)/X = 1 and X+Y = 19 or 20)

(b) hybridizing the sequences (B') and (D') with the newly synthesized sequences (Bc) and (Dc), respectively, thereby making sequences (A) and (C) single stranded (see Figure 1, step 3 and paragraph 118; see also paragraph 77)

(c) annealing primers having the same sequence as the first and second primers of step (a)

to sequences (A) and (C) obtained in step (e) above and conducting strand displacement

polymerization to displace the complementary strands obtained in step (d) and synthesize new

complementary strands (see paragraph 118 and Figure 1, steps 4-5; see also paragraph 77).

Regarding claim 10, Rabbani teaches that the double-stranded nucleic acids obtained in

step (f) are repeatedly used in step (e) (see paragraphs 77 & 118; see also Figure 1).

Regarding claim 11, Rabbani teaches that the first and second complementary nucleic

acids obtained in step (f) as single-stranded nucleic acids are used repeatedly as template nucleic

acids in step (d) (see Figure 2, step 4 and paragraph 77).

Regarding claims 22 and 23, the primers have an X+Y value of 19 or 20 in the absence of

an intervening sequence between (Ac') and (B') or (Cc') and (D') (see above), which is less than

100.

In the method of Rabbani, the primers have an X+Y value of 19 or 20 (see above), which

lies outside of the range recited in independent claims 1 and 9 (*i.e.* 30-50). Also, in the method

of Rabbani, the value of X-Y/X = 1, which lies outside of the range recited in independent claims

1 and 9 (*i.e.* -1.00 to 0.75).

Notomi teaches a method for isothermally amplifying DNA using primers (FIP and BIP)

that form stem-loop structures after extension (see abstract, pages ii-iv, and Figure 1). Like the

primers of Rabbani, the FIP and BIP primers of Notomi comprise a region that is complementary

to the template and a region that is complementary to a portion of the primer extension product

(see pages ii-iv and Figure 1). Regarding claims 1 and 9, Notomi teaches that the size of the

loop formed between the FIP or BIP primer and the primer extension product, which corresponds

to the recited Y value, is critical to the efficiency of the amplification method, and that a loop of

40 bases or longer gave the best results (page v, column 1). Notomi also teaches that the FIP and

BIP primers used in the method have an intervening sequence, which corresponds to the recited

Y' parameter, located between the (Ac') and the (B') regions of the primer (see page ii, column

1, where an intervening sequence that is four nucleotides in length is taught). In the method of

Notomi, the FIP and BIP primers have a template complementary region (*i.e.* an X value) of

approximately 22-24 nucleotides (see page ii). Thus, the loop mediated amplification reaction

Notomi utilizes primers having an X+Y value of 76 and 78 and an X-(Y-Y')/X value of -0.96 and

-1.18 (see page ii and Figure 2A on page iv). The X-(Y-Y')/X value of -0.96 taught by Notomi

lies within the claimed range of -1.00 to 0.75. The other X-(Y-Y')/X value and the values of

X+Y+Y' taught by Notomi lie outside of the claimed ranges.

Nagamine teaches methods of conducting loop mediated isothermal amplification (see

abstract and pages 224-225). Regarding claims 1 and 9, the method of Nagamine utilizes

primers (FIP and BIP) having a 3' region that is complementary to the template nucleic acid and

a 5' region that is complementary to a portion of the extension product generated upon extension

of the 3' region of the primer (see pages ii-iv and Figure 1). The FIP and BIP primers used in the

method of Nagamine have X+Y values that fall within the claimed range (see pages 224-225 and

Figure 1, where the FIP and BIP primers of Nagamine have X+Y values of 43 and 45,

respectively, and X-Y/X values of 0.35 and 0.20, respectively).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of

invention to apply the teachings of Notomi and Nagamine to the method taught by Rabbani. An

ordinary artisan would have been motivated to optimize the length of the loop formed by the

primer taught by Rabbani, since Notomi taught that this parameter was critical to achieving

optimal amplification efficiency (page v, column 1). An ordinary artisan would have recognized

from the teachings of Notomi that the length of the template-complementary portion of the

primer (*i.e.* the recited X value), the length of the loop formed by the primer with the extension

product generated during polymerase-mediated primer extension (*i.e.* the recited Y value) and

the length of any intervening sequence these regions of the primer (*i.e.* the recited Y' value) were

results-effective variables, the optimization of which was critical to practice of the method of

Rabbani. Therefore, an ordinary artisan would have been motivated to perform routine

experimentation to determine the optimal ranges for these parameters with a reasonable

expectation of success. As noted in MPEP 2144.05, citing *In re Aller*, 220 F.2d 454, 456, 105

USPQ 233, 235 (CCPA 1955), "[W]here the general conditions of a claim are disclosed in the

prior art, it is not inventive to discover the optimum or workable ranges by routine

experimentation." An ordinary artisan would have been particularly motivated to select values

of X and Y giving X+Y and X-Y/X values within the claimed ranges, since Nagamine taught

that primers having X+Y and X-Y/X values within the claimed ranges were useful for

performing loop-mediated isothermal amplification reactions, such as those taught by Rabbani

and Notomi (see pages 224-225). Thus, the methods of claims 1-7 and 9-16 are *prima facie*

obvious over Rabbani in view of Notomi and further in view of Nagamine.

5.   Claims 8 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rabbani

et al. (EP 0 971 039 A2; cited previously) in view of Notomi et al. (Nucleic Acids Research

2000; 28(12): e63; cited previously) and further in view of Nagamine (Molecular and Cellular

Probes (June 2002) 16(3):223-229; cited on an IDS) and further in view of Kool, E.T. (Current

Opinion in Chemical Biology (2000) 4: 602-608; cited previously).

The combined teachings of Rabbani, Notomi, and Nagamine result in the methods of

claims 1-7 and 9-16, as discussed above.

Rabbani, Notomi, and Naganine do not teach that target nucleic acid sequence in the

template nucleic acid comprises non-natural nucleotides as required by claims 8 and 17.

Kool teaches methods of using modified DNA templates as substrates for DNA

polymerases. Kool teaches that DNA polymerases can accept synthetic modifications to the

template or newly synthesized strand (page 602, column 2). Kool further teaches that templates

containing nucleotides with altered hydrogen-bonding capabilities may be amplified by DNA

polymerase (page 604). Kool teaches that the presence of these non-native nucleotides in the

template strand directs non-specific incorporation of any of the four natural bases into the newly

synthesized strand, which is useful for mutagenesis (page 604).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of

invention to conduct the amplification method resulting from the combined teachings of

Rabbani, Notomi, and Nagamine using a template containing non-natural nucleotide. An

ordinary artisan would have been motivated to do so, because Kool taught that the inclusion of

such nucleotides in the template strand was useful for mutagenesis applications (see page 604).

Since Kool further taught a number of specific examples of non-native nucleotides that could be

recognized and amplified by DNA polymerases (see pages 604-606), an ordinary artisan would

have had a reasonable expectation of success in utilizing a template containing non-native

nucleotides in the method resulting from the combined teachings of Rabbani, Notomi, and

Nagamine. Thus, the methods of claims 8 and 17 are *prima facie* obvious over Rabbani in view

of Notomi and further in view of Nagamine and further in view of Kool.

Response to Arguments

6.   Applicant's arguments filed on January 15, 2009 with respect to the rejection of claims 1-

7 and 9-16 under 35 U.S.C. 103(a) as being unpatentable over Rabbani in view of Notomi

remain pertinent to the new grounds of rejection made above citing Rabbani, Notomi, and

Nagamine. These arguments have been fully considered, but they were not persuasive.

Applicant first argues that the claimed methods are unobvious, because the use of primers

having X+Y values between 30 and 50 and X-Y/Y values between -1.00 and 0.75 show

unexpectedly improved amplification properties, specifically, increased amplification efficiency,

relative to primers not satisfying these conditions (see pages 7-9). This argument and the data

provided on page 8 of the response were carefully considered. Based on the data provided on

page 8 of the response, the evidence of unexpected results does not appear to be commensurate

in scope with the claimed invention. Independent claims 1 and 9 are drawn to amplification

methods wherein the value of X+Y is between 30 and 50 and the value of X-Y/X is between -

1.00 and 0.75. The data provided by Applicant on page 8 of the response indicates that the use

of some primers having X+Y and X-Y/X values within the claimed ranges may permit the use of

a shorter amplification time (*i.e.* their use results in increased amplification efficiency), but other

primers also having X+Y and X-Y/X values within the claimed range do not appear to show the

same beneficial effect. Specifically, the use of the SY153 primers described on page 8 appears

to result in increased amplification efficiency, whereas the use of the SY160 primers does not

appear to show this effect. Therefore, the evidence of unexpected results provided by Applicant does not appear to extend over the entire claimed range (X+Y is between 30 and 50; X-Y/X is between -1.00 and 0.75). As noted in MPEP 716.02(d), "Whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the 'objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support.' In other words, the showing of unexpected results must be reviewed to see if the results occur over the entire claimed range. *In re Clemens*, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980).

MPEP 716.02(d) also states that "The nonobviousness of a broader claimed range can be supported by evidence based on unexpected results from testing a narrower range if one of ordinary skill in the art would be able to determine a trend in the exemplified data which would allow the artisan to reasonably extend the probative value thereof. *In re Kollman*, 595 F.2d 48, 201 USPQ193 (CCPA 1979)." As noted above, the evidence does not suggest that the increased amplification efficiency would extend over the entire claimed range. Since the evidence of unexpected results is not commensurate in scope with the claimed invention and since one of ordinary skill in the art would not expect the unexpected results to extend over the entire claimed range, the methods of claims 1-17 are *prima facie* obvious in view of the combined teachings of Rabbani, Notomi, and Nagamine.

Finally, the data provided on page 8 of the response does not clearly establish that an increase in amplification efficiency is correlated with X+Y and X-Y/X values within the claimed ranges. Several primer pairs having X+Y and X-Y/X values lying outside of the claimed ranges show amplification efficiencies that the same as those displayed by primers having X+Y and X-

Y/X values within the claimed ranges. Specifically, primer pairs 3-4, 5-6, and 31-32 have X+Y

and X-Y/X values that lie outside of the claimed ranges, but show amplification efficiencies that

are similar to those obtained with primer pair 33-34, which has an X+Y and X-Y/X value within

the claimed range. These data suggest that amplification efficiency is not solely determined by

the values of X+Y and X-Y/X, but that other factors, such as the properties of the template

nucleic acid (*e.g.* GC content), influence amplification efficiency. As noted in MPEP 716.01(b),

there must be a nexus between the claimed invention and the evidence of secondary

considerations. Since the evidence does not clearly establish a nexus between amplification

efficiency and the claimed X+Y and X-Y/X values, the methods of claims 1-17 are *prima facie*

obvious in view of the combined teachings of Rabbani, Notomi, and Nagamine

Applicant also argues that neither Rabbani nor Notomi teaches or suggests limiting the

range of X+Y, X+Y+Y', (X-Y)/X, or {X-(Y-Y')}/X (see page 9). This argument was not

persuasive, because Notomi expressly taught that the loop size (*i.e.* the recited Y value), the

length of the template-complementary region of the primer (*i.e.* the recited X value), and the

length of any intervening spacer region (*i.e.* the recited Y' value) were critical parameters

requiring optimization for successful practice of the method (page v, column 2). An ordinary

artisan would have recognized from these teachings of Notomi that when practicing

amplification methods utilizing similar primers (*e.g.* the method of Rabbani), these parameters

should be optimized using routine experimentation to maximize the desired results (*e.g.* specific

and efficient isothermal amplification). Also, as discussed above, an ordinary artisan would have

been particularly motivated to utilize primers in the method of Rabbani having X and Y values

producing X+Y and X-Y/X values within the claimed range, since Nagamine taught that primers

analogous to the primers taught by Notomi and Rabbani having X+Y and X-Y/X values within the claimed range were useful for conducting loop-mediated amplification reactions (pages 224-225).

Applicant further argues that Notomi teaches away from the claimed values of X+Y and X-Y/X (page 9). This argument was not persuasive, because Notomi only teaches that the parameters should be optimized and does not actively disparage, discredit, or discourage the use of other lengths for the regions corresponding to the claimed X and Y values (see MPEP 2123 and 2145). Furthermore, as discussed above, the teachings of Nagamine (see pages 224-225) would have suggested to the ordinary artisan the use of primers having X and Y values that produced X+Y and X-Y/X values within the claimed ranges.

Regarding the rejection of claims 8 and 17 under 35 U.S.C. 103(a) as being anticipated by Rabbani in view of Notomi and further in view of Kool, Applicant argues that the teachings of Kool do not remedy the deficiencies of the primary combination of references (*i.e.* Rabbani and Notomi) with respect to independent claims 1 and 9 (see page 10). This argument was not persuasive, because as discussed above, the combined teachings of Rabbani, Notomi, and Nagamine render obvious the methods of claims 1-7 and 9-16.

Conclusion

7.   No claims are currently allowable.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Iwamoto et al. (Journal of Clinical Microbiology (2003) 41(6): 2616-2622) teaches

methods of conducting loop-mediated isothermal amplification using primers having X+Y and

X-Y/X values that lie within the claimed ranges (see pages 2616-2618 and Figure 1).

Applicant's amendment necessitated the new ground(s) of rejection presented in this

Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE

MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this

final action.

Any inquiry concerning this communication or earlier communications from the

examiner should be directed to ANGELA BERTAGNA whose telephone number is (571)272-

8291. The examiner can normally be reached on M-F, 9- 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the

organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent

Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR

system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would

like assistance from a USPTO Customer Service Representative or access to the automated

information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

amb

/Kenneth R Horlick/

Primary Examiner, Art Unit 1637